(1) Scientific Abstract

Ovarian cancer is predominantly an intraperitoneal tumor and thus provides a confined microenvironment to study tumor progression and therapeutic intervention. Ovarian cancer afflicts 23,000 women each year with approximately 12,000 deaths/yr. Chemotherapy (cis-platin, taxol) and surgery is the first line treatment for patients with this disease and 40-60% achieve clinical remission. However, once a patient with ovarian cancer relapses, there is no therapy that will prolong survival in these patients since the tumor is resistant to chemotherapy even though many patients in relapse recur with minimal disease.

In 1991 we have developed the first phase I clinical trial based on HSV-TK suicide gene therapy which treats ovarian cancer. Our study is based on the fact that the dying GCV exposed tumor cells were toxic to nearby unmodified tumor cells both in *in vitro* and *in vivo* studies and this observation has been termed the "bystander effect". Currently, four other institutions, both nationally and internationally have asked to and/or participate in this study (University of Rochester, Brown University, Kings College, University Laval).

Fourteen patients have been treated on this study. To date, we have shown that there is minimal toxicity, with fever being the most common side effect associated with the inoculation of up to $3x10^9$ PA-1STK gene-modified cells i.p. Two patients have achieved complete remission as evidenced by loss of ascites and normalization of the serum CA125. These patients are disease free for sixteen and seven months.

Furthermore, pre-clinical studies have shown that tumor immunization enhances the "bystander effect". Based on the pre-clinical studies and the phase I results, we are initiating a phase I/II trial. Ovarian cancer patients in relapse who express the HER-2/Neu protein on their tumor cells will be immunized to HER-2/Neu using a tumor cell line (MDA-B7) expressing HER-2/Neu and the B7 co-stimulatory molecule. Six weeks following immunization, patients will receive an i.p. inoculation of HSV-TK gene-modified cells and ganciclovir. We hypothesize, based on our animal models, that the use of HSV-TK gene therapy enhances the host's ability to respond to a tumor antigen because it alters the cytokine milieu within the tumor. The strength of this clinical trial is that a defined antigen, HER-2/Neu, is being studied. We will test whether the host's responsiveness to this antigen is enhanced using tumor immunization and HSV-TK gene therapy by measuring the CTL precursor frequency to HER-2/Neu in a limiting dilution analysis. We will also assay for effects of our treatment on the tumor by assaying for cytokine expression and changes in cells infiltrating the tumor.